APPARATUS FOR DETECTING TUMOR CELLS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a national phase application and claims the benefit under 35 U.S.C. §371 of PCT/US2012/036551, filed on May 4, 2012, which in turn claims priority to U.S. Application No. 61/482,900, filed on May 5, 2011, the contents of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

A tumor is an abnormal growth of body tissue and can be cancerous (malignant) or noncancerous (benign). Tumors, particularly cancerous tumors, are a serious threat to human well-being and their detection in early stage is critical in order to obtain effective treatment or cure. However, it is a huge challenge for conventional tumor detection methods to detect cancer earlier than symptomatically, or detect cancer at earlier stages of tumor metastasis. For example, conventional methods fail to identify about 40% of cancer patients who are in need of more or enhanced therapies. It is also important to detect any early signs of spread in cancer following cancer treatments to assess effectiveness of the treatment, as well as if and what follow-up treatment is needed. Conventional cancer detection techniques such as x-ray imaging and nuclear magnetic resonance (NMR) imaging fail to provide reliable information to the above critical applications.

Recent research and clinical studies have shown that cancer invasion to a human body may occur very early in tumor development. Early detection and early systemic therapies will result in a declining death rate from cancer. Metastasis, initiated by tumor cells transported through the circulation from the primary tumor to vital distant organs, is known to be the leading cause of cancer related deaths. The early spread of tumor cells to lymph nodes or bone marrow in peripheral blood is referred to as circulating tumor cells (CTCs or CTC). CTCs may still exist in a patient' peripheral blood even after the removal of the primary tumor.

CTCs are essential for establishing metastasis, and detection of CTCs is an important tool to assess the aggressiveness of a given tumor and its potential of subsequent growth at distant organs. Specific and sensitive detection of CTCs can be used to identify the overall cancer development or metastasis status, survival possibility, and assessment of the therapeutic response.

With more and more research on CTCs in recent years, its importance to cancer progression gets highly respected. However, CTCs exist in blood only on the order of 1 per billion to 10 billion. Present technique to separate and identify CTCs, on one hand, is quite labor intensive and expensive, and on the other hand lack accuracy and reliability. The procedure includes density gradient separation, immunomagnetic separation and density gradient immunomagnetic separation, and more hard work in dealing with the identification of the large volume filtered cells by human.

There is a pressing need to find solutions that can bring enhanced sensitivity, specificity, efficiency, convenience, and speed in early-stage CTC detection at reduced costs.

SUMMARY OF THE INVENTION

The present invention in general relates to a class of innovative methods and apparatus for detecting tumor cells, particularly circulating tumor cells (CTCs), by analyzing a biological subject (e.g., peripheral blood samples or other body fluids samples of a mammal), then diagnosing the cancer development or metastasis status thereof. It can also communicate with CTCs, and modify or correct certain aspects of CTCs. This invention utilizes novel micro-devices or an apparatus with micro-devices integrated onto it for carrying out diagnosis at microscopic levels, in vivo or in vitro, on the biological subject (e.g., fluidic samples such as blood or lymph) containing cells, (e.g., white and red blood cells, tumor cells). The apparatus can have multiple and enhanced functionalities due to the integrated micro-devices. These apparatus can be made by using state-of-the-art micro-device fabrication technologies and novel process flows such as integrated circuit fabrication technologies. Apparatus of this invention containing multiple micro-devices that can detect multiple parameters of a biological subject to be analyzed. These CTC detection apparatus are capable of detecting cancer diseases at their early stages with a high degree of sensitivity, specificity, speed, convenience (e.g., reduced equipment size), or affordability (e.g., reduced costs). Examples of cancers that can be detected by these apparatus include prostate cancer, lung cancer, colon cancer, breast cancer, brain cancer, cervical cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, kidney cancer, leukemia, liver cancer, ovarian cancer, skin cancer, testicular cancer, thyroid cancer, pancreatic cancer, endometrial cancer, esophageal cancer, and uterine cancer.

Key component of the detection equipment is a class of novel micro-devices and their inventive fabrication process flows which enable it to perform at a much higher level than those of conventional disease detection equipments or technologies, due to much improved detection sensitivity, specificity, and speed. Examples of fabrication techniques that can be used to make the micro-devices described herein include but not limited to mechanical, chemical, chemical mechanical, electro-chemical-mechanical, electro-bio-chemical-mechanical, integrated circuit and semiconductor manufacturing techniques and processes. For a general description of some of the applicable fabrication technologies, see, e.g., R. Zaouk et al., Introduction to Microfabrication Techniques, in *Microfluidic Techniques* (S. Minteer, ed.), 2006, Humana Press; *Microsystem Engineering of Lab-on-a-chip Devices,* 1st Ed. (Geschke, Klank & Telleman, eds.), John Wiley & Sons., 2004. Micro-device functionalities would at least include sensing, detecting, measuring, diagnosing, monitoring, and analyzing for disease diagnosis. Multiple micro-devices can be integrated onto a piece of detection apparatus for further enhanced measurement sensitivity, specificity, speed and functionalities, with ability to measure the same parameter or a set of different parameters.

Optional components of the apparatus include components for addressing, controlling, forcing, receiving, amplifying, or storing information from each probe. Such components can be, e.g., a central control unit that includes a controlling circuitry, an addressing unit, an amplifier circuitry, a logic processing circuitry, a memory unit, an application specific chip, a signal transmitter, a signal receiver, a sensor, a micro-electro-mechanical device, a multi-functional device, or a micro-instrument to perform surgery, drug delivery, cleaning, or medical function.

Specifically, one aspect of this invention provides apparatus for detecting CTCs in a biological subject, each comprising a first micro-device and a first substrate supporting the first micro-device, wherein the first micro-device contacts a biological entity to be analyzed and is capable of measuring at the microscopic level an electrical, magnetic, electromag-